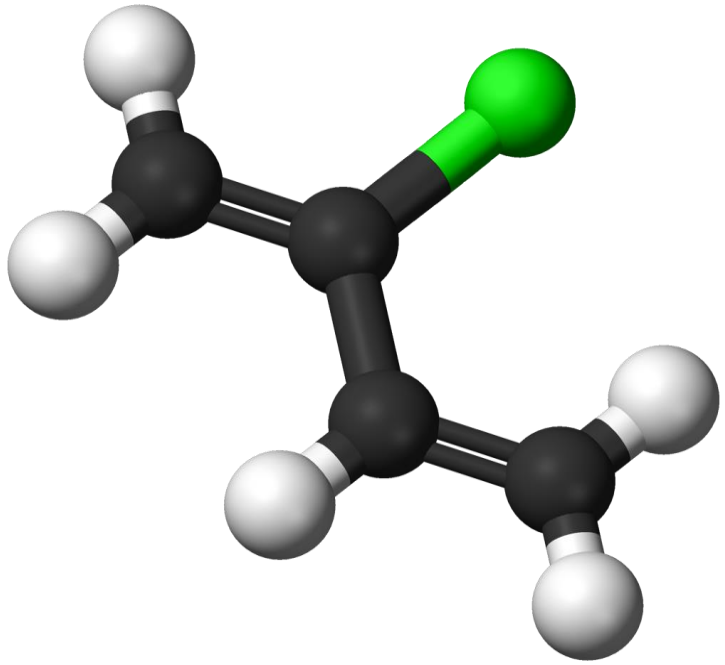
**DRAFT PRESENTATION**

# REQUEST FOR CORRECTION OF THE EPA'S 2010 IUR FOR CHLOROPRENE

**Kenneth A. Mundt, PhD, FACE**

**P. Robinan Gentry, PhD, DABT**

**Sonja Sax, ScD**



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# EXECUTIVE SUMMARY 1

- EPA published the IRIS Toxicological Review of Chloroprene in 2010, with an inhalation unit risk (IUR) of 5 x $10^{-4}$ per $\mu g/m^3$.
- This is the 5$^{th}$ highest IUR derived by IRIS for any chemical classified by IARC as carcinogenic (Group 1) or probably carcinogenic (Group 2a).
- IARC classified chloroprene as possibly carcinogenic (Group 2b).
- Ramboll Environ was requested to conduct a detailed review of the 2010 IRIS, and to derive an IUR for Chloroprene.

# EXECUTIVE SUMMARY 2

- **Key Findings: All lines of evidence indicate that the IUR should be corrected:**
- The highest quality epidemiological studies demonstrated no excess lung or liver cancer risk.
- Toxicological data do not support a mutagenic mode of action.
- Multiple lines of evidence indicate large differences between across species.
- Using NRC best practices recommendations, EPA methods and pharmacokinetic data, the Ramboll Environ IUR is 156 times lower than the 2010 IRIS IUR.
- Cancer risk estimates based on the Ramboll Environ IUR are consistent with the epidemiological data.

# INTRODUCTION

- EPA published the IRIS Toxicological Review of Chloroprene* in 2010, with an inhalation unit risk **(IUR) of 5 x $10^{-4}$ per $\mu g/m^3$**.
- Denka Performance Elastomer (DPE) acquired the Neoprene production facility in LaPlace, Louisiana from DuPont on November 1, 2015.
- On December 17, 2015, EPA published the 2011 National Air Toxics Assessment (NATA), including a risk assessment based on facility's emissions and the 2010 IRIS IUR.
- The NATA study identified DPE's facility as associated with **one of the highest offsite cancer risks** of any chemical facility in the US.
- DPE retained Ramboll Environ to evaluate the scientific validity of the 2010 IRIS IUR.
- Using EPA standard methods and publicly available data, Ramboll Environ determined that the 2010 IRIS **IUR is overestimated by a factor of 156**.

* U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/010F, 2010.

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# OBJECTIVES

- Evaluate the 2010 IRIS Review of Chloroprene, especially the IUR, in light of NRC (2011, 2014) guidance on improving IRIS assessments:
  - How studies are evaluated: quality assessment and weighting
  - Better integration of data across all lines of evidence
- Critically review and integrate the published epidemiological, toxicological, and mode of action evidence on chloroprene carcinogenicity.
- Apply a standard pharmacokinetic correction to the chloroprene IUR.
- Provide a "reality check" for the IUR.

# EPIDEMIOLOGICAL EVIDENCE

# COMPARISON OF KEY CRITERIA ACROSS STUDIES

| Key Criteria | US and Europe (Marsh *et al.* 2007) | Armenia (Bulbulyan *et al.* 1999) | Russia (Bulbulyan *et al.* 1998) | China (Li *et al.* 1989) |
|---|---|---|---|---|
| **Sample Size** | 12,430 | 2,314 | 5,185 | 1,258 |
| **Follow-up** | 1949–2000 | 1979–1993 | 1979–1993 | 1969-1983 |
| **Exposure Assessment** | Exposure modeling – 7 categories | Index (none, low, high)- before/after 1980 | Index (none, med, high)- IH (inadequate) + job | High vs. low based on recall |
| **Baseline rates** | National, local plant area counties 1960–1994 | Armenian rates 1980-1989 | Moscow rates 1979–1993 or 1992–1993 (liver) | From "local area" 1973–1975 expected lung cancers: 0.4 |
| **Confounding** | Used local rate comparisons; Low prevalence of other liver cancer risk factors | Alcohol use (high cirrhosis rates) and smoking prevalent | Alcohol use (high cirrhosis rates) and smoking; Co-exposure to VC | Hepatitis B and aflatoxin; Co-exposures to VC |

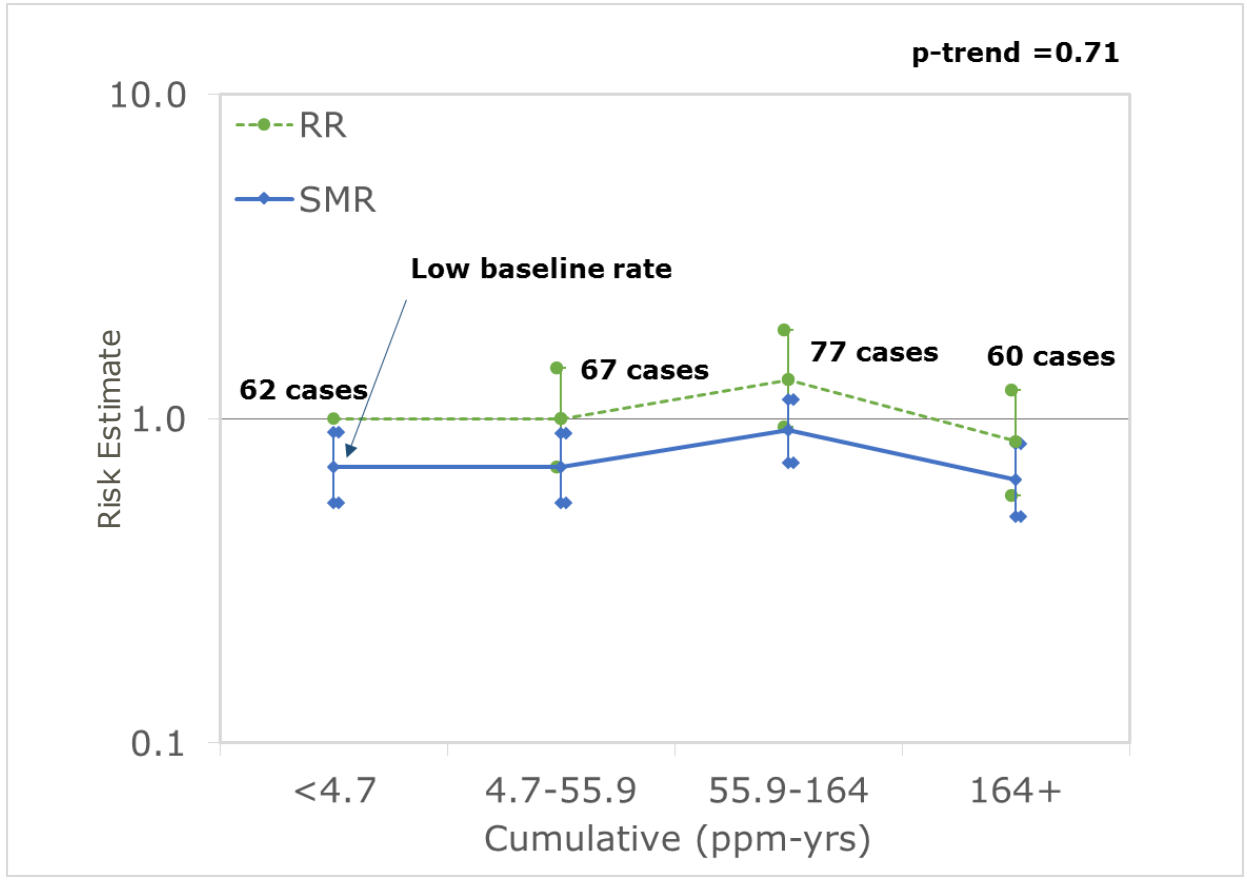
# MARSH ET AL. (2007) STUDY FINDINGS SHOULD HAVE GREATEST WEIGHT

| US EPA Criteria | Marsh et al. (2007 a,b) Study | | | | Other Studies | | | |
|---|---|---|---|---|---|---|---|---|
| | Kentucky[1] | North Ireland | Louisiana[1] | France-Mortality[1] | Armenia[2] | France-Incidence[3] | Russia[4] | China[5] |
| Clear objectives | H‡ | H | H | H | H | H-M | H | M |
| Comparison groups | H | H-M | H-M | M | M | M | M-L | L |
| Exposure | H | H | H | H | M | M | L | L |
| Follow-up | H | H-M | H | H-M | M-L | M-L | M-L | M-L |
| Case ascertainment | H | H-M | H-M | H-M | M | M | M | H-M |
| Control of bias | H-M | H-M | H-M | M | M-L | M | M | M-L |
| Sample size | H | H | M | L | M-L | L | H-M | M-L |
| Data collection and evaluation | H | H | H | H | M | M | M-L | M-L |
| Adequate response | H | H | H | H | M | M | M | H-M |
| Documentation of results | H | H | H | H | M-L | M | M | L |
| **Overall rank (1=best)** | **1** | **2** | **3** | **4** | **5** | **5** | **5** | **6** |

Source: Bukowski 2009 ‡ Subjective estimate of study quality for each specific criterion H=high, M=medium, L=low; 1 – Marsh et al. 2007; 2 – Bulbulyan et al. 1999; 3 – Colonna and Laydevant 2001; 4 – Bulbulyan et al. 1998; 5 – Li et al. 1989

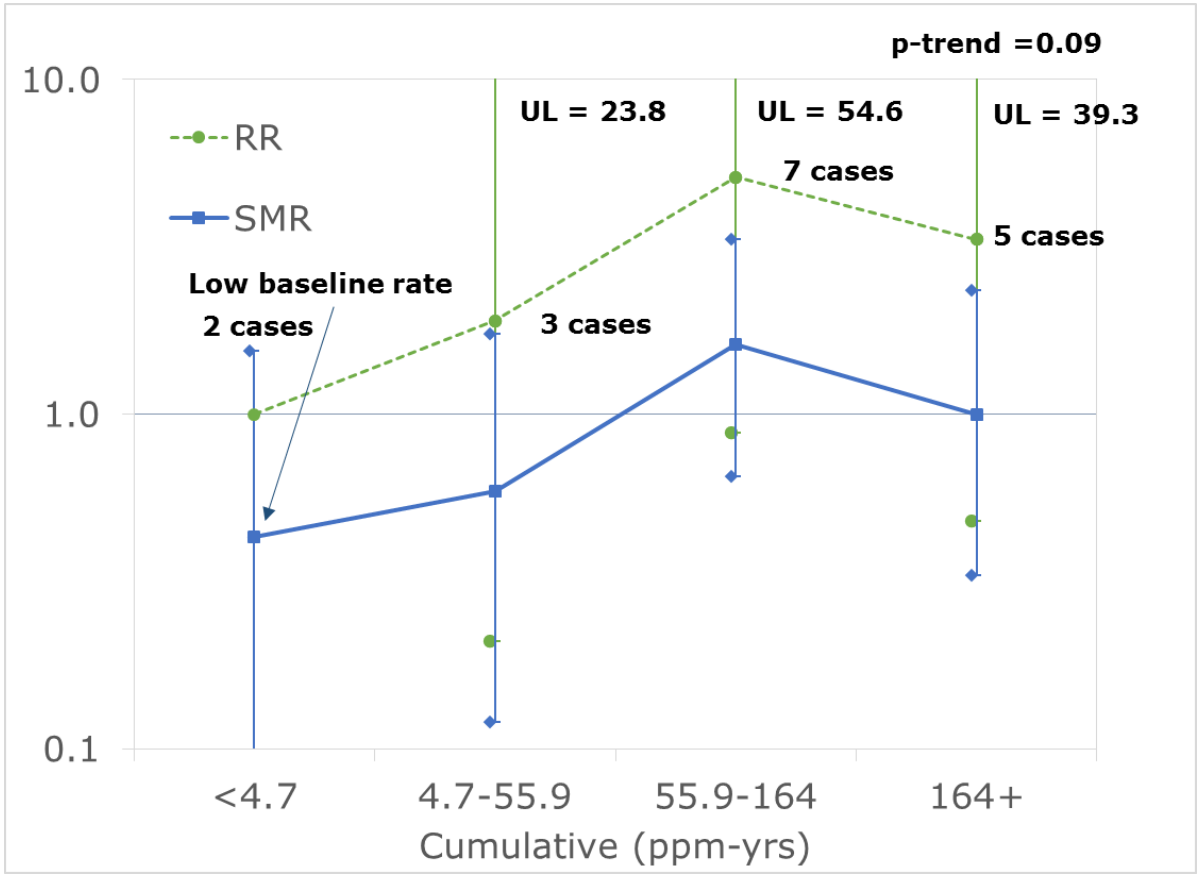
# MARSH STUDY SHOWS NO INCREASED LUNG OR LIVER CANCER RISKS

Respiratory cancers RRs and SMRs by cumulative chloroprene exposure, Louisville plant




Source: Marsh 2007b

Liver cancers RRs and SMRs by cumulative chloroprene exposure, Louisville plant




Source: Marsh 2007b

# LOCAL COMMUNITY-LEVEL CANCER RATES

- Cancer incidence data from the Louisiana Tumor Registry for St. John the Baptist Parish (where DPE plant is located) and for the state of Louisiana
- Five most recent years

| Cancer site | Parish Rate | State Rate | Ranking (1=lowest cancer rate) |
|---|---|---|---|
| All cancers | 463.2 | 478.7 | 15/64 |
| Respiratory cancers | 60.1 | 70.5 | 7/64 |
| Liver cancers | < 3 cases (too few to report) | | Unknown* |

*Unknown as as there were 28 parishes with too few liver cancer cases

Source: https://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=22&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName=rate&sortOrder=default#results

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# OCCUPATIONAL CANCER RATES IN THE PONTCHARTRAIN FACILITY, LA

- Marsh et al. (2007a) results for 1,357 workers at the Pontchartrain facility in LA (US and local reference rates)

| Cancer site | US-based SMR | Local-based SMR |
|---|---|---|
| All cancers | 0.74 (0.51-1.04) | 0.68 (0.47–0.95) |
| Respiratory cancers | 0.72 (0.37-1.26) | 0.62 (0.32-1.09) |
| Liver cancers | None reported | None reported |

# MARSH ET AL. (2007) CONCLUSION

Marsh et al. (2007) should be given greater weight than studies from Asia, Russia and Armenia:

"*We conclude that persons exposed to chloroprene or vinyl chloride at the levels encountered in the four study sites* ***did not have elevated risks of mortality from any of the causes of death*** *examined, including all cancers combined and lung and liver cancer, the cancer sites of a priori interest.*"

"*This* ***conclusion is corroborated by our detailed analyses of mortality*** *in relation to* ***qualitative and quantitative exposures to CD*** *and VC at each of the four study sites.*"

*Source: G.M. Marsh et al. / Chemico-Biological Interactions 166 (2007) 285–300*

# TOXICOLOGICAL EVIDENCE

# ANIMAL STUDIES

- Studies conducted in B6C3F1 mice and Fischer rats (NTP, 1998), and in Wistar rats and Syrian hamsters (Trochimowicz et al., 1998) at chloroprene concentrations ranging from 10 to 80 ppm.
- A significant incidence of tumors seen across many organ sites, primarily in mice and at the highest exposure levels.
- The most sensitive species/tumor site is the female mouse and the lung.
- Fewer tumors in Wistar rats and Syrian hamsters; little consistency across species both in the number of tumors and in tumor location.
- Differences in tumor incidence can be explained by using PBPK modeling and the calculated internal dose of metabolized chloroprene.

# SUMMARY OF ANIMAL DATA

| Species | Exposure concentration (ppm) | PBPK internal dose (mg/g) | Lung tumor incidence | Number of animals |
|---|---|---|---|---|
| Syrian Hamster (Trochimowicz et al., 1998) | 0 | 0 | 0 | 100 |
| | 10 | 0.18 | 0 | 97 |
| | 50 | 0.88 | 0 | 97 |
| Wistar rat (Trochimowicz et al., 1998) | 0 | 0 | 0 | 97 |
| | 10 | 0.18 | 0 | 13 |
| | 50 | 0.89 | 0 | 100 |
| Fischer rat (NTP, 1998) | 0 | 0 | 3 | 50 |
| | 12.8 | 0.22 | 3 | 50 |
| | 32 | 0.55 | 6 | 49 |
| | 80 | 1.37 | 9 | 50 |
| **B6C3F1 mouse** (NTP, 1998) | **0** | **0** | **15** | **50** |
| | **12.8** | **3.46** | **32** | **50** |
| | **32** | **5.3** | **40** | **50** |
| | **80** | **7.18** | **46** | **50** |

# EVIDENCE OF GENOTOXICITY

*In vitro* mutagenicity results are inconsistent

| Study | Method | Exposure | Response |
|---|---|---|---|
| Bartsch *et al*., 1979 | Desiccator | 4 hours | + |
| Westphal *et al*., 1994 | Pre-incubation | 2 hours | - |
| NTP, 1998 | Pre-incubation | 20 min. | - |
| Willems, 1980 | Desiccator | 24-48 hours | + |

*In vivo* results are mostly negative, and mutagenicity profile is different from 1,3-butadiene

| Chemical | ***In Vivo* (B6C3F1 mouse)** | | |
|---|---|---|---|
| | **CA** | **SCE** | **MN** |
| Chloroprene | - | - | - |
| 1,3 - Butadiene | + | + | + |

CA – chromosome aberrations; SCE - sister chromatid exchange; MN - micronucleus test; Source: Tice 1988

Weight of evidence is not consistent with a mutagenic MOA. An alternative MOA should be considered in accordance with EPA and NRC guidelines.

# CHLOROPRENE IUR

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# IUR INCONSISTENCIES

| Compound (Year of Review) | IUR per ug/m$^3$ | Basis | PBPK adjustment | Classification | Ratio |
|---|---|---|---|---|---|
| Chloroprene (2010) | **5 x 10$^{-4}$** | Multiple tumors in mice, mutagenic MOA | No | Possibly Carcinogenic | 1 |
| 1,3 Butadiene (2002a) | 3 x 10$^{-5}$ | Human occupational studies | No | Known Carcinogen | ~20 |
| Benzene (2002b) | 2 x 10$^{-6}$ – 7.8 x 10$^{-6}$ | Human occupational studies | No | Known Carcinogen | 250 |
| Vinyl Chloride (2000) | 4.4 x 10$^{-6}$ | Liver tumors in rats | Yes | Known Carcinogen | ~100 |

Adjusted IUR of chloroprene is more in line with other known carcinogens; e.g., VC IUR is based on animal data, but with PBPK model adjustments.

# UNCERTAINTIES IN THE 2010 IUR

| Step | IUR per ug/m³ | Basis |
|---|---|---|
| **Most sensitive endpoint/species (portal-of-entry DAF=1.7)** | $1.06 \times 10^{-4}$ | Lung tumors in female mice as a portal-of-entry effect |
| **Most sensitive endpoint/species (systemic lesion DAF=1)** | $1.81 \times 10^{-4}$ | Lung tumors in female mice as a systemic effect |
| **Multiple tumor adjustment** | $2.7 \times 10^{-4}$ | Multiple tumors |
| **Rounding** | $3 \times 10^{-4}$ | Rounding |
| **Application of ADAF** | **$5 \times 10^{-4}$** | Adjustment |

# PHARMACOKINETIC CORRECTION OF THE ANIMAL DATA

| | IUR per ug/$m^3$ | Basis | Resulting decrease in IUR |
|---|---|---|---|
| US EPA (2010) | **$5 \times 10^{-4}$** | Fully adjusted composite value in female mice with ADAF correction | Referent |
| Allen et al. (2014) | $1.86 \times 10^{-6}$ | PBPK dosimetric adjustment of lung tumors in female mice in target organ; includes animal and human data | ~250 fold decrease |
| Ramboll Environ (2017) | $3.2 \times 10^{-6}$ | PBPK dosimetric adjustment of lung tumors in female mice in the target organ; based on animal data only | 156 fold decrease |

# PHARMACOKINETIC CORRECTION OF THE CHLOROPRENE IUR

- PBPK model was published by Himmelstein et al. (2004).
- Data were provided to EPA at the time of the review to check the validity of the model; however, EPA did not incorporate these data into the final IUR estimate.
- Data provided to EPA have been published (Yang et al., 2012; Thomas et al., 2013).
- Allen et al. (2014) reported that an IUR that incorporates pharmacokinetic differences 250 times lower than the 2010 IRIS IUR.
- Using the internal dose estimates from PBPK modeling from Yang et al. (2012) Ramboll Environ derived an IUR of **$3.2 \times 10^{-6}$** per $\mu g/m^3$ which is **156 times lower** than the 2010 IRIS IUR.

# "REALITY CHECK"

| Source | Unit Risk (per ppm) | Mean Exposure* (ppm) | Excess Cancers (Risk Estimate) | Excess Cancers (Observed–Expected) Local referent |
|---|---|---|---|---|
| US EPA (2010) lung tumor | 0.65 | 8.42 | 5.5 | -84 (lung)<br>-1.9 (liver) |
| multi tumor | 1.08 | 8.42 | 9.1 | |
| w/ADAF | 1.80 | 8.42 | 15.2 | |
| Allen et al. (2014) lung tumor | 0.0067 | 8.42 | 0.06 | |
| Ramboll Environ lung tumor | 0.012 | 8.42 | 0.1 | |

*Mean exposure reported by Marsh et al. 2007a

IUR corrected for pharmacokinetic differences results in a cancer risk estimate consistent with epidemiological results (i.e., no observable excess risk).

# CANCER CLASSIFICATION

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# CANCER CLASSIFICATION OF CHLOROPRENE

EPA classified chloroprene as "likely to be a human carcinogen" based on:

- National Toxicology Program (NTP, 1998) chronic inhalation bioassay;
- Associations between chloroprene exposure and liver cancer in four of nine epidemiological studies;
- Limited evidence of lung cancer;
- Proposed mutagenic mode of action; and
- Analogies with 1,3-butadiene and vinyl chloride

*Critical review of the evidence indicated that four of these five cannot be substantiated.*

*The classification should be revisited and a clearer narrative provided.*

https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1021

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# SUMMARY AND CONCLUSIONS

# BASES FOR A REQUEST FOR CORRECTION OF THE 2010 IUR

- The highest quality epidemiological studies do not demonstrate a causal relationship between occupational exposures to chloroprene and cancer.
- Many lines of evidence point to pharmacokinetic differences across species.
- PBPK modeling is the best approach for correcting the IUR because of large pharmacokinetic differences between the mouse and humans.
- Using PBPK model output and standard EPA methods, Ramboll Environ calculated an IUR that is 156 times lower than the 2010 IRIS IUR.

**Integration of the full body of evidence indicates that the pharmacokinetic differences between the mouse and humans require that the IUR be corrected using PBPK model results.**

# THANK YOU

Ken Mundt

kmundt@ramboll.com

Robinan Gentry

rgentry@ramboll.com

Sonja Sax

ssax@ramboll.com